



## REVIEW

# Cellular and Molecular Insights into the Pathophysiology of Obesity-Related Asthma

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**ABSTRACT:** Obesity-related asthma is a distinct clinical phenotype, characterized by severe respiratory symptoms, reduced responsiveness to conventional glucocorticoid therapy, and a significantly increase in disease burden. With the rising global prevalence of obesity, the number of individuals affected by obesity-related asthma is steadily growing, presenting a pressing public health issue. The pathogenesis of obesity-related asthma is multifactorial, involving a complex interplay of metabolic and immune pathways. Key mechanisms include dysregulated T-cell differentiation, pro-inflammatory macrophage polarization, oxidative stress, and altered cytokines and adipokines secretion, all contributing to airway inflammation and remodeling. Additionally, metabolic factors, such as adiposity and adipokine imbalance, further complicated disease progression. A major clinical challenge is developing targeted therapies to address the substantial heterogeneity in this patient population. Current treatment approaches, largely focused on corticosteroids, often fail to achieve satisfactory outcomes, emphasizing the need for novel, tailored therapies that target the specific pathophysiological features of obesity-related asthma. This review systematically explores the cellular and molecular mechanisms driving obesity-related asthma, focusing on how obesity-associated factors such as adipokines and airway remodeling influence disease progression. The review also evaluates emerging therapeutic interventions and highlights the ongoing challenges in clinical diagnosis and management. By synthesizing recent research, this study aims to provide insights into potential strategies for improving treatment and clinical outcomes for patients with obesity-related asthma.

**KEYWORDS:** Obesity-related asthma; airway inflammation; airway remodeling; immune dysregulation; cytokine networks

## 1 Introduction

Asthma is a heterogeneous respiratory disorder characterized by chronic airway inflammation, airway hyperresponsiveness (AHR), and reversible airflow limitation, predominantly affecting the lower respiratory tract. It presents clinically with recurrent episodes of wheezing, dyspnea, chest tightness, and cough, often exacerbated at night or in the early morning, triggered by allergens, respiratory infections, cold air, exercise, and other environmental factors [1,2].

Obesity has been firmly established as an independent risk factor for asthma development [3]. Consistent with global epidemiological trends, asthma prevalence has risen in parallel with the obesity epidemic,



and accumulating evidence highlights a strong association between the two conditions [4–7]. In a large cohort of 60,639 individuals aged 25–74 years, 30.8% of incident asthma cases in women and 19.2% in men were attributable to overweight and obesity [8]. The rising prevalence of obesity globally has paralleled the increase in asthma cases, and childhood obesity in particular has become a significant concern. According to the World Health Organization, nearly 35 million children under five years of age were overweight or obese in 2024, with over 390 million school-aged children affected in 2020. This alarming trend highlights the growing challenge of obesity-related asthma. This distinct and treatment-refractory phenotype is characterized by poor disease control, reduced quality of life, and an increased risk of acute exacerbations. Despite its increasing clinical recognition, targeted therapeutic strategies for this phenotype remain limited [9].

Obesity contributes to both the initiation and progression of asthma through several interrelated mechanisms, primarily involving mechanical, inflammatory, and metabolic pathways. First, mechanical constraints from excessive thoracic adiposity increase chest wall load and airway resistance, thereby reducing lung volumes and impairing pulmonary function [10]. Prolonged exposure to mechanical stress can independently trigger airway remodeling. *In vitro* studies show that mechanical compression induces goblet cell hyperplasia, enhances extracellular matrix deposition, and promotes release of mediators such as endothelin-1 and chitinase-3-like protein 1, which drive airway smooth muscle proliferation [11]. Clinically, the decline in the forced expiratory volume in the first second (FEV1)/forced vital capacity (FVC) ratio is a critical marker of airflow obstruction, and has been closely related to asthma incidence, with studies showing a strong association between obesity and airflow limitation in both children and adults [12,13].

Second, immuno-inflammatory pathways play a central role in obesity-related asthma. Visceral adipose tissue in obesity individuals becomes enriched with macrophages that polarize toward the pro-inflammatory M1 phenotype [14–16]. These macrophages release cytokines such as Interleukin-1 Beta (IL-1 $\beta$ ), Tumor Necrosis Factor Alpha (TNF- $\alpha$ ), and Interleukin (IL)-8, which disrupt the pulmonary immune microenvironment, promote neutrophil chemotaxis, and skew T-cell differentiation, driving Th1/Th2/Th17 imbalance and amplifying airway inflammation [17,18].

Third, obesity induces metabolic dysfunction characterized by altered adipokine secretion and oxidative stress, further exacerbating airway pathology [19]. Elevated leptin levels correlate with asthma onset and severity [20,21], while reduced adiponectin weakens its anti-inflammatory effects [22,23]. Additionally, resistin overproduction promotes insulin resistance and systemic inflammation, further aggravating airway inflammation in asthma [24,25]. In parallel, excessive generation of reactive oxygen species impaired antioxidant defenses, promoted lipid peroxidation, and directly injured the airway epithelium, thereby driving airway remodeling and hyperresponsiveness [26].

This review aims to systematically investigate the multifactorial mechanisms through which obesity contributes to asthma, with a particular focus on mechanical constraints, immune-inflammatory pathways, and endocrine-metabolic dysregulation. By synthesizing recent advances, this study seeks to clarify the intricate interactions between metabolic and immune factors that exacerbate asthma pathogenesis. Additionally, the review evaluates the clinical challenges and diagnostic complexities associated with obesity-related asthma, emphasizing the need for more precise and tailored therapeutic strategies, as well as improved diagnostic tools, to better manage this increasingly prevalent condition. By providing an integrated perspective on its pathophysiology, this review aims to inform the development of emerging therapeutic strategies, potentially enabling precision-based interventions to improve outcomes for affected individuals.

## 2 From Immune Cells and Cytokines to Molecular Pathways and Tissue Crosstalk

### 2.1 The Role of Immune Cells

#### 2.1.1 Macrophage Polarization and Its Implications in the Pathogenesis of Obesity-Related Asthma

Macrophages are abundant immune cells in the lungs and play a central role in maintaining tissue homeostasis [27]. Increasing evidence highlights their significant role in asthma pathogenesis. Data from the U-BIOPRED cohort, which analyzed sputum samples from 104 asthmatic patients and 16 healthy controls, revealed that macrophage counts were significantly lower in patients with severe asthma compared to mild-to-moderate cases and healthy controls [28]. Similarly, in obese asthmatic mice, reduced macrophage proportions were observed in bronchoalveolar lavage fluid, alongside more severe airway inflammation [29]. These findings suggest that asthma progression may be linked to macrophage immunodeficiency, although the exact mechanisms are yet to be fully elucidated. Macrophages exhibit two principal activation states: M1 (classically activated) and M2 (alternatively activated). In obesity-related asthma patients, the M1/M2 ratio in visceral adipose tissue is elevated, accompanied by altered macrophage morphology and function [30,31]. M1 polarization drives the release of pro-inflammatory cytokines, contributing to systemic low-grade inflammation and metabolic dysfunction. Studies show that obesity-related asthma patients display increased circulating IL-6 levels, further supporting the role of macrophage-driven inflammation in asthma [32,33]. In addition to systemic effects, M1 polarization profoundly influences airway inflammation. The proportion of M1 macrophages in sputum correlates with neutrophil counts, highlighting the close relationship between macrophage polarization and airway neutrophilia. Furthermore, M1 macrophages promote Th1 and Th17 differentiation by secreting pro-inflammatory cytokines such as IL-12 and IL-23, thus amplifying neutrophil-driven inflammation [34].

#### 2.1.2 Immunological Dysregulation of T Cells and B Cells in the Pathogenesis of Obesity-Related Asthma

CD4<sup>+</sup> T cells are central to the immunopathology of asthma. Although asthma was once regarded primarily as an allergic disease mediated by Th2 cells, this view is now recognized as overly simplistic. Asthma pathogenesis is complex and can be broadly classified into allergic and non-allergic phenotypes, or alternatively into “type 2-high” and “type 2-low” asthma, based on underlying immune mechanisms [35]. The former is driven predominantly by type 2 inflammation, often triggered by allergen exposure, and involves not only Th2 cells but also other immune cells that release type 2 cytokines. In contrast, type 2-low asthma is mediated by non-type 2 inflammatory pathways, the mechanisms of which remain incompletely understood but seem to be influenced by factors such as obesity and environmental pollution [2]. The prevalence of these phenotypes also varies with age, with allergic asthma most common in childhood, whereas non-allergic asthma tends to increase with aging [36]. Obesity-related asthma is considered a prototypical type 2-low phenotype, marked by enhanced Th1/Th17 polarization of CD4<sup>+</sup> T cells [37–39]. In this context, CD4<sup>+</sup> T-cell subsets undergo significant reprogramming, which includes the upregulation of cell division cycle 42 expression, enhancement of Th1-driven inflammatory responses, and downregulation of the glucocorticoid receptor gene (NR3C1), all contributing to the distinct obesity-related asthma phenotype [40,41]. Clinical studies further support this: randomized controlled trials in children show that dexamethasone-induced FK506 binding protein (FKBP) 51 expression in CD4<sup>+</sup> T cells strongly correlates with poorer asthma control in obese patients [42]. Similarly, transcriptomic analyses of obesity-related asthma have revealed upregulation of several molecular signatures, such as IL-7R, IL-32, poly (ADP-ribose) polymerase-1, FKBP5, elevated IL-6 levels, and activation of the Rho signaling pathway [43]. At the cellular level, peripheral CD4<sup>+</sup> T-cell subsets in obese children with asthma show a skewed distribution, characterized by an increased proportion of memory T cells and a decreased proportion of naïve T cells. Notably, the Rho-GTPase signaling

pathway is enriched in Th cells from this population [44]. The role of CD8<sup>+</sup> T cells in asthma is less well understood, though emerging evidence suggests that certain CD8<sup>+</sup> T-cell subsets may contribute to airway pathology by mediating tissue inflammation and recurrent airway damage via effector molecules such as granzyme K [45].

B cells play a pivotal role in allergic asthma by producing IgE antibodies upon allergens exposure [46]. In addition to IgE production, B cells contribute to immune regulation through IL-10 secretion, which has dual effects: it suppresses activation of certain immune cells and stimulates lung epithelial cells to produce the chemokine C-C motif chemokine ligand 20 (CCL-20). CCL-20 facilitates dendritic cells recruitment to the lungs, thereby amplifying Th2-mediated immune responses and worsening airway hyperresponsiveness and mucus secretion [47]. In obesity, however, the proportion of regulatory B cells is reduced, resulting in low IL-10 secretion, impaired immune tolerance, and a skewing toward Th1/Th17-driven inflammation [48,49]. Clinical evidence supports this: a cohort of 168 children with asthma showed that those in the obese/overweight subgroup had significantly lower serum IL-10 levels compared to children with asthma alone ( $8.69 \pm 2.76$  pg/mL vs.  $15.32 \pm 6.28$  pg/mL), highlighting the role of obesity in aggravating immune dysregulation in asthma [50].

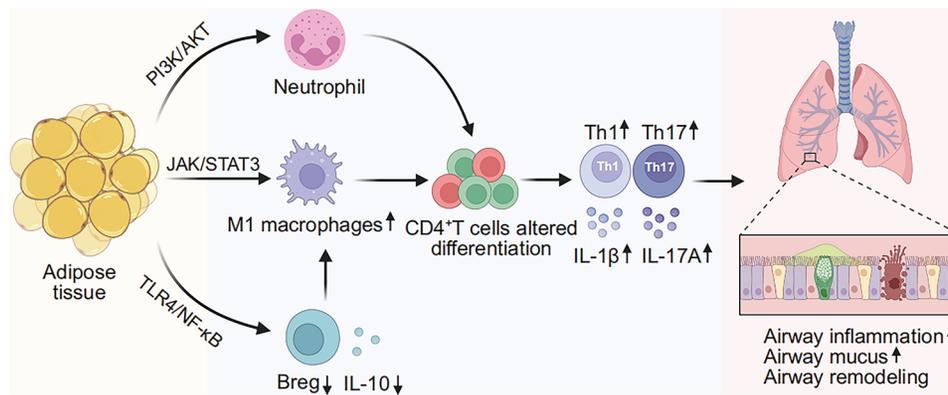
### 2.1.3 The Role of Neutrophils in Obesity-Related Asthma

Excessive lipid accumulation in adipose tissue induces adipocyte stress and dysfunction, which trigger inflammatory responses. Neutrophils, the most abundant white blood cells in circulation, are the first immune cells to infiltrate adipose tissue, where they further activate the immune system by releasing inflammatory mediators and recruiting macrophages and other leukocytes [51]. A meta-analysis of 4475 participants found that both absolute neutrophil count and the neutrophil-to-lymphocyte ratio were elevated in obese individuals compared to normal-weight controls. Notably, the absolute neutrophil count showed greater divergence from controls, lower heterogeneity among obese subjects, and a strong positive correlation with body mass index (BMI) [52]. Beyond systemic circulation, obesity is also linked with gut microbiota dysbiosis and impaired intestinal barrier integrity, allowing translocation of live bacteria, bacterial DNA, lipopolysaccharides, and pro-inflammatory cytokines into the bloodstream and adipose tissue. These changes contribute to metabolic inflammation, further modulate neutrophil activation, migration, and mediator release. Clinically, adult-onset asthma (first onset >15 years) with non-type 2 inflammatory features, such as obesity and elevated blood neutrophils, has been strongly associated with poor asthma control and increased requirements for inhaled corticosteroids (ICS) [53]. Consistent with these findings, obesity-related asthma patients exhibit a ~5% higher proportion of sputum neutrophils compared to non-obese counterparts [54]. Animal models further corroborate that obesity exacerbates asthma development and progression through non-Th2 inflammatory pathways characterized by neutrophil infiltration [29,39]. A schematic diagram summarizing the proposed mechanism is presented in Fig. 1.

## 2.2 Cytokines and Signaling Pathways

In addition to immune cell reprogramming, cytokine networks and signaling pathways further amplify obesity-related airway inflammation. The NF- $\kappa$ B signaling pathway is regulated by the Rel protein family, which includes c-Rel, NF- $\kappa$ B1 (p105/p50), NF- $\kappa$ B2 (p100/p52), RelA (p65), and RelB, forming transcriptionally active complexes through dimerization [55]. Under basal conditions, NF- $\kappa$ B is inactive in the cytoplasm, bound to the inhibitor of kappa B (I $\kappa$ B). Upon cellular stimulation, I $\kappa$ B undergoes phosphorylation and degradation, releasing NF- $\kappa$ B to translocate to the nucleus and initiate transcription of downstream target genes [56]. Notably, selective activation of NF- $\kappa$ B alone has been shown to replicate key pathological features of allergic airway disease, such as AHR and smooth muscle thickening [57]. In obesity-related

asthma, oxidative stress and reactive oxygen species-mediated cellular injury activate p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK), driving NF- $\kappa$ B overactivation and persistent production of inflammatory mediators such as IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 [58–60]. These cytokines amplify the inflammatory cascade by promoting M1 macrophage polarization and Th17 differentiation in lung tissues [61,62]. As a central transcription factor in the TLR4 signaling pathway, NF- $\kappa$ B not only enhances pro-inflammatory mediator production but also establishes a positive feedback loop with NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome-mediated pyroptosis [63]. Experimental studies suggest that blocking this axis confers therapeutic benefit; for example, Involucrin B has been shown to alleviate airway inflammation in obesity-related asthma models by inhibiting the TLR4/NF- $\kappa$ B/NLRP3 pathway [64]. Clinical evidence supports these findings, demonstrating that activation of the TLR4/MyD88/NF- $\kappa$ B pathway facilitates NLRP3 inflammasome assembly, thereby exacerbating neutrophil infiltration and pyroptosis-associated airway injury in asthma patients [65]. As a transcriptional hub in the TLR4 signaling axis, NF- $\kappa$ B also amplifies inflammation through crosstalk with the NLRP3 inflammasome, contributing to neutrophil infiltration and pyroptosis-associated airway injury.



**Figure 1:** Adipose tissue-mediated immune dysregulation in obesity-related asthma. Adipose tissue-driven immune dysregulation in obesity-related asthma, characterized by increased M1 macrophages, enhanced neutrophil infiltration, and reduced regulatory B cells/IL-10, contributes to impaired CD4<sup>+</sup> T cells differentiation and the worsening of airway inflammation, mucus hypersecretion, and airway remodeling. IL-10, interleukin-10. IL-1 $\beta$ , interleukin-1 $\beta$ . IL-17A, interleukin-17A. Breg, regulatory B cell. Th1, T helper 1 cell. Th17, T helper 17 cell, PI3K, phosphoinositide 3-kinase. AKT, protein kinase B. JAK, Janus kinase. STAT3, signal transducer and activator of transcription 3. TLR4, toll-like receptor 4. NF- $\kappa$ B, nuclear factor kappa-light-chain-enhancer of activated B cells. Figures were created with biorender.com

Building on this, the hallmark of obesity-related asthma is a chronic, low-grade inflammatory state sustained by abnormal adipose tissue accumulation and overactivation of cytokines, particularly IL-6 and TNF- $\alpha$  [66,67]. This process involves three interconnected mechanisms. First, hypertrophic adipose tissue releases excess free fatty acids (FFAs), activating the TLR4/NF- $\kappa$ B signaling axis, inducing M1 macrophage polarization, and stimulating cytokine secretion [68,69]. Second, an elevated leptin-to-adiponectin ratio enhances macrophage activity via the JAK-STAT3-PI3K/AKT pathway, promotes C-X-C motif chemokine ligand 2 (CXCL2)-driven neutrophil recruitment, and diminishes the anti-inflammatory role of adiponectin [29,70,71].

Third, hypoxic stress and the induction of hypoxia-inducible factor 1- $\alpha$  amplify cytokine release, further intensifying systemic inflammation. These pro-inflammatory mediators collectively disrupt epithelial barrier integrity, increase mucus hypersecretion (MUC5AC) expression, promote type I and III collagen deposition, and accelerate airway remodeling [72,73]. Importantly, IL-6 and TNF- $\alpha$  synergize to promote

Th17 differentiation and IL-17A release, sustaining neutrophilic inflammation and tissue injury [74–78]. Clinically, elevated serum and sputum IL-6 and TNF- $\alpha$  levels in obesity-related asthma patients correlate with accelerated lung function decline and glucocorticoid resistance [50,79–81]. Systemic inflammatory patterns, similar to those observed during respiratory crises at the population level, contribute to disease exacerbation and reduced therapeutic responses due to immune dysregulation. In the context of COVID-19, Nazari et al. emphasized the importance of immune-inflammatory control strategies in managing respiratory crises [82]. Their findings highlight the critical role of effective immune modulation in preventing exacerbations and improving therapeutic outcomes, offering valuable insights that could inform the management of obesity-related asthma.

### 2.3 Crosstalk between Adipose Tissue and Airway Inflammation

In obesity, adipocyte hypertrophy and dysfunction drive macrophage recruitment and polarization toward a pro-inflammatory state, contributing to distal airway injury [16,19]. Central to this “adipose-lung axis” is the ability of adipose-derived factors to modulate the pulmonary immune microenvironment and structural cells via systemic circulation or local paracrine signaling. This section outlines the molecular mechanisms, effector targets, and potential therapeutic strategies of adipose secretion-mediated airway inflammation (see Table 1).

**Table 1:** Fat secretions mediate airway inflammation

Category of fatty secretions	Key molecules	Mechanism of action	Inflammatory effects of the airways	Pathological outcomes
Lipotoxic mediator	FFAs	Induce neutrophil production of NETs [83]	Dendritic cell activation and T cell differentiation are affected	The proportion of Th1 and Th17 cells increased, and the release of IL-1 $\beta$ , IL-12 and TNF- $\alpha$ increased
Adipokines	Leptin	JNK/STAT3/AKT pathway activation $\rightarrow$ enhances M1 macrophage polarization $\uparrow$ [29]; Affects the frequency of distribution of CD4 $^+$ T cell subsets [84,85]	CXCL2 $\uparrow$ $\rightarrow$ Enhanced neutrophil infiltration; The Th17/Treg ratio increased, and the CD4 $^+$ T cell subset was imbalanced	Increased airway neutrophilic inflammation and resistance to glucocorticoid therapy
	Adiponectin	AMPK pathway inhibition $\rightarrow$ Anti-inflammatory effect $\downarrow$ [86–89]	IL-10 secretion $\downarrow$ , Inflammation is blocked from subsiding	Chronic inflammation persists

(Continued)

**Table 1 (continued)**

Category of fatty secretions	Key molecules	Mechanism of action	Inflammatory effects of the airways	Pathological outcomes
Inflammatory cytokines	IL-6	SFK-YAP axis activated → Fibroblast proliferation [75]	The basement membrane thickens, collagen is deposited	Airway fibrosis remodeling
	TNF- $\alpha$	MUC5AC $\uparrow$ [72] → MMP-9/MMP-12 expression $\uparrow$ [73]	↑ Epithelial integrity is disrupted, elastic fibers degrade	Emphysema-like changes and airway collapse

**Note:** FFAs, free fatty acids. NETs, neutrophil extracellular traps. Th1, T helper 1. Th17, T helper 17. IL-1 $\beta$ , interleukin-1 $\beta$ . IL-12, interleukin-12. TNF- $\alpha$ , tumor necrosis factor alpha. JNK, c-Jun N-terminal kinase. STAT3, signal transducer and activator of transcription 3. AKT, protein kinase B. CXCL2, C-X-C motif chemokine ligand 2. Treg, regulatory T cells. AMPK, AMP-activated protein kinase. SFK-YAP, Src family kinases—Yes-associated protein. MUC5AC, Mucin 5AC. MMP-9, matrix metalloproteinase-9.

### 3 Clinical Manifestations and Diagnostic Challenges in Obesity-Related Asthma

#### 3.1 Clinical Heterogeneity

Obesity-related asthma is recognized as a distinct phenotype characterized by elevated BMI, severe symptoms, and unique inflammatory features, highlighting heterogeneity within the asthma spectrum [90]. Unlike classical allergic asthma, this phenotype shows weak associations with atopy and often presents as non-allergic asthma [3,91]. Symptom burden and airflow limitation correlate with obesity severity and may persist despite minimal airway inflammation.

Standard anti-inflammatory therapies, such as ICS, often provide suboptimal control, underscoring the influence of weight-related factors [53]. Pathogenesis is multifactorial: beyond airway inflammation and bronchoconstriction, excess adiposity imposes mechanical constraints that reduce lung volumes and ventilatory capacity, leading to refractory airflow obstruction poorly responsive to bronchodilators [90,92]. Inflammatory profiles also differ. Classical asthma is typically type 2–high with eosinophilia and elevated IL-4, IL-5, and IL-13 [93], whereas obesity-related asthma is commonly neutrophilic inflammation accompanied by low-grade inflammation and increased IL-6 and TNF- $\alpha$  [29,70]. Adipokines imbalance further promotes airway inflammation and impairs responses to conventional therapies [70]. Management therefore, requires integrated approaches. Weight reduction and metabolic control improve symptoms and airflow limitation [94], while biologics targeting IL-6 and TNF- $\alpha$  represent potential strategies for addressing non-T2 inflammation [9]. Overall, the distinct clinical manifestations, non-T2 predominance, and reduced responsiveness to conventional therapy emphasize the need for combined weight management and individualized anti-inflammatory interventions to optimize patient outcomes and quality of life.

#### 3.2 Diagnostic Challenges

The heterogeneous manifestations of obesity-related asthma make its diagnosis a significant clinical challenge. Its symptoms often overlap with other asthma phenotypes, and obesity-induced mechanical constraints and metabolic abnormalities further complicate recognition. Olejnik AE and Kuźnar-Kamińska B reported that reduced chest wall compliance, decreased lung volumes, and systemic metabolic inflammation in obesity contribute to atypical airflow limitation and worsened clinical outcomes, particularly evident in

pulmonary function [95]. Reyes Noriega et al. noted that lung function tests often reveal obstruction not fully explained by airway inflammation but strongly influenced by the mechanical burden of obesity, limiting the diagnostic accuracy of conventional spirometry [96]. Another challenge is inflammatory heterogeneity: unlike classical asthma, which is typically T2-high, obesity-related asthma often presents with a systemic pro-inflammatory response. Picado et al. demonstrated that elevated IL-6 and TNF- $\alpha$  are closely associated with this phenotype [70], while experimental models have revealed enhanced non-T2 pathways such as IL-17, TNF- $\alpha$ , and transforming growth factor beta (TGF- $\beta$ ) with neutrophilic infiltration, but without increases in classical T2 cytokines like IL-5 and IL-13, highlighting its distinctive inflammatory profile [39]. These differences reduce the utility of conventional biomarkers and single inflammatory markers.

Diagnostic complexity is further compounded by comorbidities such as metabolic syndrome, diabetes, and hypertension, where chronic low-grade inflammation can obscure or exaggerate asthma symptoms, reducing the sensitivity of current criteria. As emphasized by Picado et al., systemic inflammation induced by obesity may mimic asthma and alter disease progression and therapeutic responses, rendering traditional diagnostic frameworks insufficient. Advances in omics offer new opportunities: Björkander et al. reported that plasma metabolite and inflammatory marker profiles in obesity-related asthma differ markedly from those in non-obese individuals, supporting the use of metabolomics for subtype identification [33]. Popović-Grle et al. highlighted that future precision diagnosis will require integration of clinical features, lung function, biomarkers, metabolomics, and emerging imaging techniques to establish personalized diagnostic standards [97]. As mechanistic insights grow, novel biomarkers and advanced imaging technologies hold strong potential to improve diagnostic accuracy and enhance precision medicine for this complex phenotype.

## 4 Current Clinical Management of Obesity-Related Asthma

### 4.1 Conventional Pharmacological Therapy

#### 4.1.1 ICS and Beta2-Agonists

ICS remain the cornerstone of asthma management, with strong evidence supporting their ability to suppress airway inflammation, improve lung function, and reduce exacerbations [98]. However, patients with obesity-related asthma exhibit a consistently reduced response to ICS. Even at high doses, ICS provides less clinical benefit in this subgroup compared to non-obese patients [94]. This reduced efficacy is linked to the low-T2 inflammatory profile characteristic of obesity-related asthma, which is defined by reduced eosinophil counts, low fractional exhaled nitric oxide (FeNO), absence of allergic drivers, and a decreased need for maintenance oral corticosteroids (OCS) [99]. Furthermore, Li et al. emphasized that obesity-induced mechanical load and metabolic dysregulation significantly influence airway obstruction, both of which may diminish ICS effectiveness [100].

Beta2-agonists are commonly used to provide rapid relief of acute asthma symptoms [101]. However, their efficacy is reduced in obesity. Elevated plasma FFAs, a common feature in obesity, activate G protein-coupled receptors (GPCRs) such as GPCR40 and GPCR120, triggering inflammatory cascades that enhance airway hyperresponsiveness and reduce bronchial smooth muscle responsiveness to beta2-agonists [102]. Additionally, the mechanical load caused by obesity promotes structural remodeling of airway smooth muscle, further impairing its sensitivity to bronchodilators. Obesity-associated low-grade inflammation, marked by elevated IL-6 levels, may also exacerbate airway dysfunction and reduce the effectiveness of bronchodilators [81].

#### 4.1.2 *Leukotriene Receptor Antagonists (LTRAs)*

LTRAs, such as montelukast, target the CysLT1 receptor and block leukotriene-mediated pathways, including airway constriction, mucus secretion, and inflammatory cell infiltration. These agents have been used to treat conditions like exercise-induced bronchoconstriction, allergic rhinitis, and aspirin-exacerbated respiratory disease [103]. In obesity, excessive leptin secretion from adipose tissue leads to elevated circulating leptin levels [29]. Experimental studies show that leptin enhances cysteinyl leukotriene production in rat alveolar macrophages [104]. Additionally, obesity is associated with increased expression of 5-lipoxygenase and its activating 5-lipoxygenase-activating protein, which boosts leukotriene synthesis, particularly leukotriene B4, within adipose tissue. This amplifies both local and systemic inflammatory responses [105]. These findings support the use of LTRAs in obesity-related asthma. Indeed, Farzan et al. reported that montelukast treatment significantly improved Asthma Control Test (ACT) scores and asthma control in patients with early-onset atopic obesity-related asthma [106]. However, while these results suggest potential benefits, further randomized controlled trials are needed to confirm the efficacy of LTRAs in this phenotype.

### 4.2 *Future Perspectives on Targeted Therapy*

#### 4.2.1 *Bruton's Tyrosine Kinase (BTK) Inhibitors*

BTK is a key signaling molecule expressed in B cells and myeloid cells such as macrophages, mast cells, and neutrophils. It regulates cellular activation and inflammatory mediators release [107]. BTK inhibitors block signaling downstream of the B-cell receptor (BCR), Toll-like receptors (TLRs), and Fc receptors, thereby suppressing excessive immune responses. These agents show therapeutic potential in autoimmune, allergic, and inflammatory diseases, including asthma [108]. In a murine mixed-granulocytic asthma model, ibrutinib suppressed both neutrophilic and eosinophilic inflammation, reduced Th2 cytokine production, and lowered immune activation markers [109]. In obesity-related asthma, airway tissues show increased eosinophil and neutrophil infiltration, suggesting a complex mixed-granulocytic phenotype [110,111]. In a high-fat-diet-induced obese mouse model, ibrutinib attenuated NF- $\kappa$ B and NLRP3 inflammasome-driven inflammation, lowered fasting glucose, and improved glucose tolerance, indicating additional benefits in obesity-associated metabolic dysregulation [112]. Taken together, these findings provide a mechanistic rationale for BTK inhibitors as potential therapeutics in obesity-related asthma. However, current evidence is preliminary, and further studies and clinical trials are required [113].

#### 4.2.2 *Anti-IgE Therapy*

Anti-IgE monoclonal antibodies, such as omalizumab, block free IgE from binding to its receptor Fc $\epsilon$ RI, preventing mast cells and basophils activation [114]. In two randomized controlled trials, omalizumab reduced asthma exacerbations by 71.9% in obese patients (BMI  $\geq$  30 kg/m<sup>2</sup>), with efficacy comparable to non-obese groups [115]. A prospective study also reported that 12 months of omalizumab therapy improved asthma control and, for the first time, was linked to better lung function in obese patients [116]. Similar results were observed by Pilkington et al., confirming favorable clinical responses [117]. Collectively, these findings support anti-IgE therapy as an effective treatment option for obesity-related asthma.

#### 4.2.3 *IL-5 Inhibitors and Related Biologic Therapies*

IL-5 drives eosinophil differentiation and activation, making it central in type 2-high asthma. Monoclonal antibodies targeting IL-5 reduce eosinophil counts in the circulation and airways, improving lung function and reducing exacerbation [118,119]. IL-13 also contributes to airway remodeling by promoting

goblet cell hyperplasia, mucus hypersecretion, smooth muscle hypertrophy, and fibrosis. Blocking IL-13 or its downstream pathways can reduce these changes and potentially improve long-term outcomes [120]. In obesity-related asthma, elevated IL-5, IL-17A, and IL-25 expression suggests multiple inflammatory cascades contribute to disease [121]. Although no dedicated trials have yet assessed the efficacy of anti-IL-5 or anti-IL-13 antibodies in obesity-related asthma, mechanistic evidence supports their therapeutic potential, especially in patients with eosinophilic or type 2 inflammatory features.

#### **4.3 Obesity-Targeted and Lifestyle Interventions**

Recent studies show that patients with obesity-related asthma often present with T2-low or neutrophil-dominant inflammatory phenotypes. These are characterized by elevated levels of IL-6, IL-17, and TNF- $\alpha$ , along with excessive NLRP3 inflammasome activation. This ultimately drives AHR and corticosteroid resistance [70,122,123]. Weight reduction therapy has been shown to ameliorate this inflammatory state through multiple mechanisms. Weight loss significantly lowers systemic inflammatory markers, such as C-reactive protein, and reduces airway inflammation [94]. Long-term follow-up after bariatric surgery consistently demonstrates sustained asthma control improvements, with reductions in pro-inflammatory adipokines like leptin and resistin, and a decrease in adipose tissue inflammation [124]. Lifestyle interventions combining dietary modification with physical exercise have also been shown to decrease circulating IL-6 and TNF- $\alpha$  levels, improving asthma control and lung function in a relatively short period [125].

In addition to lifestyle changes, pharmacological interventions show promise. Glucagon-like peptide-1 receptor agonists (GLP-IRAs) provide dual benefits by promoting weight reduction and exerting independent anti-inflammatory effects. In a murine model of obesity-related asthma, liraglutide significantly reduced AHR and eosinophilic inflammation, while also suppressing NLRP3 inflammasome activation and IL-1 $\beta$  expression in bronchial tissues. It also led to marked reductions in IL-4, IL-5, and IL-33 levels in bronchoalveolar lavage fluid [126]. Similarly, Kaplan et al. found that patients receiving GLP-IRAs had fewer asthma exacerbations. The abundant expression of GLP-1 receptors in lung tissues supports the anti-inflammatory activity of GLP-IRAs [127]. Overall, weight reduction improves chest wall compliance through mechanical unloading and induces immunometabolic reprogramming, significantly alleviating airway inflammation in obesity-related asthma. This reinforces the role of weight management as a cornerstone of comprehensive disease management.

### **5 Conflicting Evidence and Unresolved Mechanistic Controversies**

#### **5.1 Inconsistent Associations between BMI and Asthma Phenotypes across Ethnic Groups**

The relationship between BMI and asthma risk varies significantly across populations, both in the strength and shape of the association (linear, U-shaped, or threshold effects). For example, data from China and the United States show distinct patterns. In elderly populations in China (CHARLS), a U-shaped relationship is observed, where both low and high BMI correlate with increased asthma risk. In contrast, the United States (NHANES) shows a nonlinear “threshold-after-increase” relationship in the same age group, suggesting a different optimal BMI for asthma risk across populations [128]. In pediatric populations, analysis of NHANES data from 1999 to 2020 reveals a nonlinear positive association between BMI and asthma. However, stratified analyses demonstrate variations in this relationship based on racial and socioeconomic subgroups, indicating that population background may influence the strength of this association [129]. A real-world study from the Singapore Severe Asthma Registry, which includes multiple ethnic groups (Chinese, Malay, and Indian), found higher obesity-related comorbidities among non-Chinese patients, with poorer asthma control. Phenotypic clustering analysis revealed ethnic differences, indicating that the “obesity-related asthma” burden is ethnicity-specific [130]. Furthermore, BMI alone may obscure population

differences. Studies based on NHANES data and bidirectional Mendelian randomization suggest a J-shaped relationship between fat distribution and adult asthma risk, with causal effects showing significant variance between populations [6]. Obesity-related asthma involves various immune and metabolic pathways and is associated with a non-eosinophilic inflammation phenotype. This phenotype is particularly pronounced in certain populations, women, and individuals with metabolic comorbidities. These differences contribute to the inconsistencies in the relationship between BMI and asthma phenotypes across populations [9].

### **5.2 Divergent Findings Regarding IL-17A's Role in Obesity-Related Asthma**

Recent studies on IL-17A's role in obesity-related asthma have produced inconsistent findings. Al Heialy et al. demonstrated that IL-17A stimulation in adipocytes from obesity-related asthma patients led to an imbalance in the GR- $\alpha$ /GR- $\beta$  ratio, suggesting that IL-17A may contribute to steroid resistance by regulating glucocorticoid receptor expression [131]. Conversely, Leija-Martínez et al. found reduced promoter methylation of the IL-17A and TNFA genes in obesity-related asthma, indicating epigenetic regulation of IL-17A expression [132]. Additionally, Buabraig et al. proposed that IL-17F, rather than IL-17A, may play a more prominent role in obesity-related asthma. The differential roles of IL-17A and IL-17F could vary across individuals, underlining the need for further research into their specific mechanisms in different populations [133]. In conclusion, IL-17A's role in obesity-related asthma remains complex, influenced by IL-17F, epigenetic factors, and individual variability. Future research should aim to clarify IL-17A's specific role and its mechanisms, to develop more precise and targeted therapies.

### **5.3 Mixed Clinical Efficacy of Biologics in Non-T2 Asthma**

Recent clinical studies have shown considerable heterogeneity in the efficacy of biologics for non-T2 obesity-related asthma. A retrospective study found that omalizumab reduced severe asthma exacerbations by approximately 60%–70% in obese patients who experienced weight loss, though the treatment effect was more pronounced in non-obese patients. This suggests that body weight may influence biologic efficacy [134]. A review by Pilkington et al. found that biologics such as dupilumab, mepolizumab, omalizumab, and tezepelumab were effective for obesity-related asthma, especially tezepelumab, which showed therapeutic benefits in patients with low-type T2 asthma [117]. However, the efficacy of biologics for non-T2 asthma remains contentious. For instance, while azithromycin and tezepelumab are available treatment options for non-T2 asthma, their efficacy and indications require further investigation [135]. Overall, the response to biologics in non-T2 obesity-related asthma is highly variable, influenced by body weight, inflammation phenotype, and comorbidities. Future research should focus on the phenotypic characteristics of obesity-related asthma and explore personalized treatment strategies to improve biologic efficacy and safety in this population.

## **6 Challenges and Future Directions**

### **6.1 Personalized Treatment Needs**

Tiotiu et al. categorized obesity-related asthma into two major phenotypes: an early-onset, allergic phenotype with more severe disease, and a late-onset, non-allergic phenotype where obesity-related chest wall loading impairs lung function. Both phenotypes often respond poorly to standard therapies, highlighting the need for individualized treatment [136]. Hudler et al. proposed that BMI should be a central factor in evaluating these patients and advocated for incorporating obesity as a treatable trait in asthma management. Defining target BMI values and promoting sustained weight reduction could improve disease control and reduce the overall burden [137]. From a precision medicine perspective, identifying obesity-related asthma endotypes should rely on an integrated comprehensive assessment of clinical manifestations,

pulmonary function, inflammatory biomarkers (peripheral blood neutrophil-to-eosinophil ratios), and metabolic status [138].

### **6.2 Emerging Pharmacological Agents and Therapeutic Strategies**

In recent years, the treatment landscape for obesity-related asthma has evolved, moving beyond traditional anti-inflammatory and bronchodilator therapies toward more diversified and precise approaches. Among the most promising strategies, cell-based therapies have gained significant attention. Mesenchymal stem cells and their extracellular vesicles are increasingly recognized for their ability to modulate abnormal inflammatory responses and promote tissue repair, offering novel therapeutic opportunities [139]. Additionally, notable advances have been made in immunomodulatory and biologic therapies. Tezepelumab, a monoclonal antibody targeting the epithelial cytokine thymic stromal lymphopoietin, has shown broad anti-inflammatory effects across various asthma phenotypes in clinical trials, suggesting potential therapeutic benefits for severe asthma complicated by obesity [140]. Natural compounds and small-molecule immunomodulators, such as celestrol,  $\gamma$ -secretase inhibitors, and C-X-C chemokine receptor type 2 (CXCR2) antagonists, have demonstrated preclinical efficacy in reducing AHR by dampening Th17-driven responses and neutrophilic inflammation [141]. Furthermore, emerging gene therapies, along with single-cell transcriptomic analyses, reveal mechanisms in obesity-related asthma, such as CDC42 upregulation, NLRP3 inflammasome activation, and NR3C1 downregulation in CD4<sup>+</sup> T cells. These insights highlight potential molecular targets for future precision therapies [40]. Together, these developments expand the therapeutic options and provide a framework for individualized management in obesity-related asthma.

### **6.3 Translational Challenges in Clinical Practice**

Obesity-related asthma presents significant therapeutic challenges. Emerging evidence suggests that face multiple therapeutic barriers in clinical practice. One major barrier is the lack of phenotype-specific recommendations in current asthma management guidelines, hindering the integration of individualized treatments into routine care [142]. A substantial body of evidence also indicates that obese patients show reduced responsiveness to ICS, highlighting the limited efficacy of conventional anti-inflammatory therapies in this subgroup [143]. Beyond pharmacological challenges, obesity exacerbates airway inflammation and structural remodeling, contributing to progressive lung function decline and increased risks of exacerbations and hospitalizations, further complicating management [121]. Of particular concern, many patients with obesity-related asthma present with an atypical T2-low inflammatory phenotype, which is generally resistant to standard treatments, and no specific therapies for this endotype are available [144]. Additionally, certain phenotypic subsets, such as those with more severe symptoms, higher prevalence among women, and poorer disease control, highlight the clinical heterogeneity and the need for precision-based approaches [33]. The primary challenges in managing obesity-related asthma involve heterogeneous drug responses, obesity-driven airway remodeling, and the lack of personalized treatment strategies. Overcoming these barriers requires a “treatable traits” framework that integrates metabolic modulation, weight management, and next-generation biologics for more precise and effective interventions.

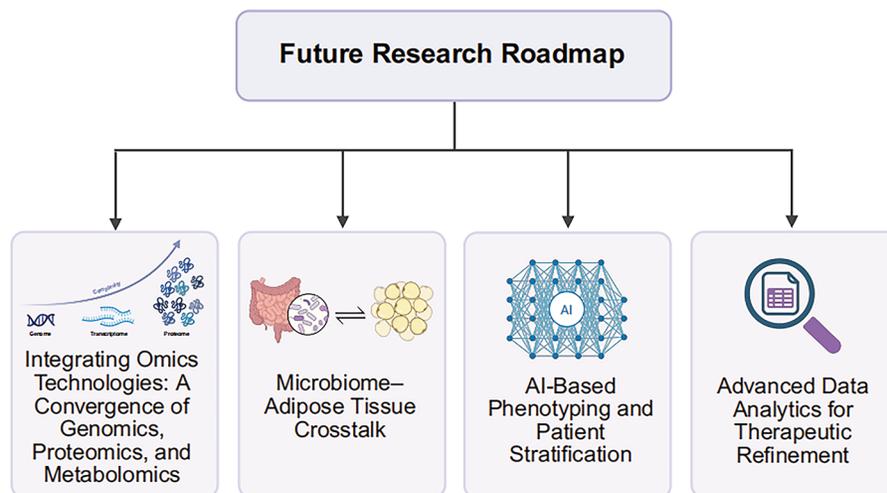
## **7 Conclusion and Outlook**

Obesity-related asthma is increasingly recognized as a distinct clinical phenotype, often characterized by non-T2 inflammation and airway remodeling, where ICS efficiency is limited. This endotype is driven by obesity-associated adipokines such as leptin, which sustain systemic inflammation, TGF- $\beta$ -mediated airway remodeling, and the mechanical burden of excess weight on lung mechanics. Emerging evidence suggests that GLP-1RAs, like semaglutide, may reduce symptoms and exacerbation risk through mechanisms

beyond weight reduction. Lifestyle modifications and weight-loss interventions have also shown consistent improvements in asthma control.

Future research should focus on the immunometabolic-airway axis and rigorously evaluate GLP-1Ras, alongside other innovative therapies, such as microbiome-targeted and receptor-specific treatment. Cross-disciplinary collaboration involving respiratory, endocrine, nutritional, and immunological disciplines is essential to advance precision management tailored to asthma endotypes. Looking ahead, future studies should prioritize the integration of omics technologies, such as genomics, proteomics, and metabolomics, to provide a more comprehensive understanding of the molecular mechanisms underlying obesity-related asthma. This integrated approach will facilitate the identification of novel biomarkers for more accurate diagnosis and personalized strategies.

Further exploration into the microbiome-adipose tissue crosstalk is crucial, as it may reveal how gut microbiota influences adipose tissue function and inflammation, offering new insights into the pathogenesis of obesity-related asthma. Additionally, utilizing AI-based phenotyping could improve patient stratification, identifying specific subtypes of obesity-related asthma based on clinical, genetic, and environmental factors. By applying advanced data analytics, we can refine therapeutic approaches and optimize outcomes for this heterogeneous patient population. These research directions hold the potential to significantly enhance our understanding of obesity-related asthma and pave the way for more effective, personalized therapies. A proposed future research roadmap is presented in Fig. 2.



**Figure 2:** Future research roadmap for obesity-related asthma. This schematic illustrates key research directions, including the integration of omics technologies, investigation of microbiome-adipose tissue interactions, AI-based phenotyping for patient stratification, and the use of advanced data analytics to optimize therapeutic approaches. These efforts are aimed at improving the understanding and treatment of obesity-related asthma. AI, artificial intelligence. Figures created with biorender.com

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